Complete Summary

GUIDELINE TITLE

HIV drug - drug interactions.

BIBLIOGRAPHIC SOURCE(S)

New York State Department of Health. HIV drug-drug interactions. New York (NY): New York State Department of Health; 2004. 34 p. [32 references]

GUIDELINE STATUS

This is the current release of the guideline.

* * REGULATORY ALERT * *

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released:

- On April 7, 2005, after concluding that the overall risk versus benefit profile is unfavorable, the U.S. Food and Drug Administration (FDA) requested that Pfizer, Inc voluntarily withdraw Bextra (valdecoxib) from the market. The FDA also asked manufacturers of all marketed prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including Celebrex (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. Finally, FDA asked manufacturers of non-prescription (over the counter [OTC]) NSAIDs to revise their labeling to include more specific information about the potential gastrointestinal (GI) and cardiovascular (CV) risks, and information to assist consumers in the safe use of the drug. See the FDA Web site for more information.

  Subsequently, on June 15, 2005, the FDA requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products. FDA recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for

products that FDA determines pose a serious and significant public health concern. See the FDA Web site for more information.

Additional Notices

- On July 8, 2005, the U.S. Food and Drug Administration (FDA) notified healthcare professionals of updated labeling for Cialis, Levitra and Viagra to reflect a small number of post-marketing reports of sudden vision loss, attributed to NAION (non arteritic ischemic optic neuropathy), a condition where blood flow is blocked to the optic nerve. FDA advises patients to stop taking these medicines, and call a doctor or healthcare provider right away if they experience sudden or decreased vision loss in one or both eyes. Patients taking or considering taking these products should inform their health care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION. Such patients are at an increased risk of developing NAION again. At this time, it is not possible to determine whether these oral medicines for erectile dysfunction were the cause of the loss of eyesight or whether the problem is related to other factors such as high blood pressure or diabetes, or to a combination of these problems. See the FDA Web site for more information.
- On January 19, 2005, the U.S. Food and Drug Administration (FDA) issued a public health advisory about recent safety-related changes to the nevirapine (Viramune®) label and about appropriate use of HIV triple combination therapy containing nevirapine. The Indications and Usage section now recommends against starting nevirapine treatment in women with CD4+cell counts greater than 250 cells/mm3 unless benefits clearly outweigh risks. This recommendation is based on a higher observed risk of serious liver toxicity in patients with higher CD4 cell counts prior to initiation of therapy. See the FDA Web site for more information.
- On June 10, 2005, Bristol-Myers Squibb and FDA notified healthcare professionals of revisions to the WARNINGS, PRECAUTIONS/Pregnancy and Information for Patients, and PATIENT INFORMATION sections of the prescribing information for Sustiva (efavirenz), indicated in the treatment of HIV-1 infection. The revisions are a result of four retrospective reports of neural tube defects in infants born to women with first trimester exposure to Sustiva, including three cases of meningomyelocele and one Dandy Walker Syndrome. As Sustiva may cause fetal harm when administered during the first trimester to a pregnant woman, pregnancy should be avoided in women receiving Sustiva. An antiretroviral pregnancy registry has been established to monitor fetal outcomes of pregnant women exposed to Sustiva. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infection
- Conditions associated with drug interactions encountered in HIV-infected patients using highly active antiretroviral therapy (HAART) as well as therapy for comorbid conditions and for prophylaxis of opportunistic infections

GUIDELINE CATEGORY

Management
Prevention
Risk Assessment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Infectious Diseases
Internal Medicine
Pharmacology

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide an overview of known and potential drug interactions encountered with the use of highly active antiretroviral therapy (HAART)
- To provide recommendations for prevention and management of these drug interactions

TARGET POPULATION

Human immunodeficiency virus (HIV)-infected patients

INTERVENTIONS AND PRACTICES CONSIDERED

1. Conducting a thorough medication history at each visit including prescription medications, over-the-counter medications, recreational drugs, and herbal and alternative therapies

2. Classifying common substrates, inducers, and inhibitors of the cytochrome P-450 (CYP450) system to predict significant drug interaction
3. Identifying of dietary restrictions with antiretroviral (ARV) drugs to avoid food-drug interactions
4. Providing patients with a detailed list of drugs contraindicated with the use of highly active antiretroviral therapy (HAART)
5. Avoiding certain drug combinations (refer to the original guideline document for details)

MAJOR OUTCOMES CONSIDERED

Morbidity/adverse effects associated with drug-drug interactions

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Human Immunodeficiency Virus (HIV) Guidelines Program works directly with committees composed of HIV Specialists to develop clinical practice guidelines. These specialists represent different disciplines associated with HIV care, including infectious diseases, family medicine, obstetrics and gynecology, among others. Generally, committees meet in person 3 to 4 times per year, and otherwise conduct business through monthly conference calls.

Committees meet to determine priorities of content, review literature, and weigh evidence for a given topic. These discussions are followed by careful deliberation to craft recommendations that can guide HIV primary care practitioners in the delivery of HIV care. Decision making occurs by consensus. When sufficient evidence is unavailable to support a specific recommendation that addresses an important component of HIV care, the group relies on their collective best practice experience to develop the final statement. The text is then drafted by one member, reviewed and modified by the committee, edited by medical writers, and then submitted for peer review.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The clinician should conduct a thorough medication history at each visit that includes prescription medications, including those prescribed by other providers, over-the-counter medications, recreational drugs, and herbal/alternative therapies.

The clinician should classify common substrates, inducers, and inhibitors of the cytochrome P-450 (CYP450) system used in highly active antiretroviral therapy (HAART) to accurately predict drugs that may lead to significant drug interactions (refer to Table below titled "Select CYP450 Inducers, Inhibitors, and Substrates").

Refer to Appendix B in the original guideline document for information on routes of elimination of HAART and the effect on CYP450.

The clinician should identify dietary restrictions with antiretroviral (ARV) drugs so that food-drug interactions can be avoided.

Key Point: Providing patients with a detailed list of drugs contraindicated with HAART may help the patient to identify significant drug interactions.

Key Point: Induction can be problematic during HAART due to concerns for virologic failure when protease inhibitors (PI) and/or non-nucleoside reverse transcriptase inhibitor (NNRTI) drug concentrations are reduced.

Select CYP450 Inducers, Inhibitors, and Substrates				
	1A2	2C19	2D6	3A4
Inducers	ritonavir rifampin phenytoin omeprazole phenobarbital nicotine	rifampin carbamazepine ritonavir efavirenz	rifampin phenytoin phenobarbital carbamazepine	efavirenz nevirapine rifampin phenytoin phenobarbital carbamazepine glucocorticoids St. John's Wort ritonavir
Inhibitors	fluoroquinolones cimetidine ticlopidine fluvoxamine amiodarone atazanavir	cimetidine ketoconazole omeprazole fluoxetine lansoprazole paroxetine	ritonavir paroxetine sertraline fluoxetine cimetidine celecoxib amiodarone quinidine methadone	protease inhibitors (PIs) (in order of potency: ritonavir indinavir nelfinavir amprenavir atazanavir saquinavir) delavirdine fluconazole ketoconazole amiodarone diltiazem fluvoxamine nefazodone fluoxetine clarithromycin erythromycin grapefruit juice Seville orange juice
Substrates	haloperidol theophylline	nelfinavir lansoprazole	metoprolol carvedilol	clarithromycin cyclosporine

Select CYP450 Inducers, Inhibitors, and Substrates				
	1A2	2C19	2D6	3A4
	zileuton amitriptyline cyclobenzaprine	omeprazole pantoprazole diazepam phenytoin voriconazole	codeine dextromethorphan tramadol venlafaxine	erythromycin alprazolam midazolam triazolam simvastatin lovastatin atorvastatin nifedipine nisoldipine felodipine PIs nevirapine efavirenz delavirdine sertraline

HAART-Related Drug Interactions

Anticonvulsants

Clinicians should monitor anticonvulsant levels in patients taking concurrent HAART and anticonvulsant therapy.

Clinicians should avoid prescribing carbamazepine, phenobarbitol, and phenytoin for patients receiving non-nucleoside reverse transcriptase inhibitors (NNRTIs) or PIs.

Antifungal Drugs

Clinicians should not prescribe voriconazole for patients taking efavirenz or ritonavir (400 mg every 12 hours). Clinicians should use caution when combining voriconazole with the other NNRTIs or PIs.

Antimycobacterial Drugs

Clinicians should not use rifampin with indinavir, nelfinavir, amprenavir, fosamprenavir, atazanavir, or lopinavir, either alone or in dual PI combinations using low-dose ritonavir (<200 mg twice daily), nor should they use rifampin with saquinavir alone.

With proper dose adjustments, rifampin can be safely used with the following drugs:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Nucleotide reverse transcriptase inhibitors (NtRTIs)
- Enfuvirtide
- Saquinavir + ritonavir
- Ritonavir + NRTIs or NtRTIs
- Efavirenz + NRTIs or NtRTIs

With proper dose adjustments, rifabutin can be safely used with the following drugs:

- NRTIs
- NtRTIs
- Amprenavir
- Atazanavir
- Enfuvirtide
- Fosamprenavir
- Indinavir
- Lopinavir/r
- Nelfinavir
- Ritonavir
- Efavirenz when used with 2 NRTIs
- Nevirapine* when used with 2 NRTIs
- Saquinavir + ritonavir

Erectile Dysfunction Agents

The following is generally recommended when erectile dysfunction agents are combined with PIs:

Sildenafil - use reduced initial dose of 25 mg every 48 hours and monitor for adverse effects

Tadalafil - use initial dose of 5 mg, and do not exceed a single dose of 10 mg in 72 hours

Vardenafil - use initial dose of 2.5 mg, and do not exceed a single 2.5-mg dose in 72 hours

Ergot Alkaloids

Clinicians should not prescribe ergotamine derivatives in patients receiving concurrent PI therapy. Alternative medications should be considered.

Herbal Therapy

In the setting of PI- or NNRTI-based HAART, supplemental garlic and St. John's Wort are contraindicated.

All herbal products should be used with caution until further data are available regarding their effects with concurrent HAART.

Key Point: In one study, only 54% of patients who were receiving HAART and using herbal therapy told their clinicians that they were using herbal therapy.

HMG-CoA Reductase Inhibitors

Clinicians should not prescribe simvastatin or lovastatin for patients taking PIs.

Key Point: Pravastatin is the safest drug for treating hyperlipidemia during concurrent PI therapy. Atorvastatin can be used cautiously at lower doses (5-10 mg) with careful titration. Rosuvastatin likely will not interact with PIs and NNRTIs.

Oral Contraceptives

Clinicians should use caution when prescribing oral contraceptives for patients receiving HAART because of the variations in effect on ethinyl estradiol levels.

Clinicians should advise women who are taking efavirenz, nevirapine, lopinavir/ritonavir, nelfinavir, ritonavir, or saquinavir to use alternate or additional forms of birth control.

Psychotropic Therapies

Drug interactions with most psychotropic therapies are summarized in Table 3 in the original guideline document.

Sedative/Hypnotics

Clinicians should not prescribe alprazolam, midazolam, triazolam, or benzodiazepines for patients receiving PIs.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Identification of risk, prevention, and appropriate management of human immunodeficiency virus (HIV) drug-drug interactions

POTENTIAL HARMS

Not stated

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Following the development and dissemination of guidelines, the next crucial steps are adoption and implementation. Once practitioners become familiar with the content of guidelines, they can then consider how to change the ways in which they take care of their patients. This may involve changing systems that are part of the office or clinic in which they practice. Changes may be implemented rapidly, especially when clear outcomes have been demonstrated to result from the new practice such as prescribing new medication regimens. In other cases, such as diagnostic screening or oral health delivery, however, barriers emerge which prevent effective implementation. Strategies to promote implementation, such as through quality of care monitoring or dissemination of best practices, are listed and illustrated in the companion document to the original guideline (HIV clinical practice guidelines, New York State Department of Health; 2003), which portrays New York's HIV Guidelines Program. The general implementation strategy is outlined below.

- Statement of purpose and goal to encourage adoption and implementation of guidelines into clinical practice by target audience
- Define target audience (providers, consumers, support service providers).
    - Are there groups within this audience that need to be identified and approached with different strategies (e.g., HIV Specialists, family practitioners, minority providers, professional groups, rural-based providers)?
- Define implementation methods.
    - What are the best methods to reach these specific groups (e.g., performance measurement consumer materials, media, conferences)?
- Determine appropriate implementation processes.
    - What steps need to be taken to make these activities happen?
    - What necessary processes are internal to the organization (e.g., coordination with colleagues, monitoring of activities)?
    - What necessary processes are external to the organization (e.g., meetings with external groups, conferences)?
    - Are there opinion leaders that can be identified from the target audience that can champion the topic and influence opinion?
- Monitor progress.
    - What is the flow of activities associated with the implementation process and which can be tracked to monitor the process?
- Evaluate.
    - Did the processes and strategies work? Were the guidelines implemented?
    - What could be improved in future endeavors?

IMPLEMENTATION TOOLS

Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

New York State Department of Health. HIV drug-drug interactions. New York (NY): New York State Department of Health; 2004. 34 p. [32 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004

GUIDELINE DEVELOPER(S)

New York State Department of Health - State/Local Government Agency [U.S.]

SOURCE(S) OF FUNDING

New York State Department of Health

GUIDELINE COMMITTEE

Medical Care Criteria Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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Liaisons: Barbara Chaffee, MD, MPH; Joseph R. Masci, MD; Noemi Nagy

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the New York State Department of Health AIDS Institute Web site.

Print copies: Available from Office of the Medical Director, AIDS Institute, New York State Department of Health, 5 Penn Plaza, New York, NY 10001; Telephone: (212) 268-6108

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- HIV drug - drug interactions. Tables and recommendations. New York (NY): New York State Department of Health; 2004 Aug. 28 p. Electronic copies: Available from the New York State Department of Health AIDS Institute Web site.

- HIV clinical practice guidelines. New York (NY): New York State Department of Health; 2003. 36 p. Electronic copies: Available from the New York State Department of Health AIDS Institute Web site.

Print copies: Available from Office of the Medical Director, AIDS Institute, New York State Department of Health, 5 Penn Plaza, New York, NY 10001; Telephone: (212) 268-6108

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on January 17, 2005. This summary was updated on April 15, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisories on Sustiva (efavirenz) and COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on July 15, 2005 following the FDA advisory on Cialis, Levitra, and Viagra.

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